

**Remarks/Arguments**

**Status of the Application**

Claim 1 is currently amended and claims 11 and 12 are hereby withdrawn from cancellation and amended to depend from claim 1 so that claims 1-5 and 7-23 are pending. Applicants note claims 11-12 were mistakenly canceled in Applicants' response to the Restriction Requirement filed February 21, 2008. The claims should have been amended to depend from claim 1 to facilitate rejoinder should claim 1 from which they depend be found allowable. Applicants apologize for the error.

**Response to Election/Restriction Requirement**

Applicants point out that Groups I, II, and III set forth in the Restriction Requirement mailed January 23, 2008 are related as product and process for making/using. As Applicants elected to pursue Group I product claims, Applicants respectfully request in accordance with MPEP § 821.04 that the Office rejoin the withdrawn process claims when the product claim from which such process claims depend is found allowable. As a result, Applicants defer canceling the Group II and III process for making/using claims until such time as the claims from which they depend are found allowable and a determination as to rejoinder made.

**Rejections under 35 U.S.C. §112, second paragraph**

Claim 1 was rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to point out and distinctly claims the subject matter which applicant regards as the invention." The Office requests clarification as to what is meant by "C<sub>6-10</sub>aryl" and "C<sub>2</sub>heteroaryl".

With regard to "C<sub>6-10</sub>aryl", Applicants acknowledge the Office's comments but respectfully assert a person of ordinary skill in the art would have readily understood the scope of the term "C<sub>6-10</sub>aryl" when viewed in light of the definition cited by the Office. In fact, the Office was readily able to discern the meaning of the term at issue. See, Office Action page 10. Indeed, section 2173.02 of the MPEP explains "[t]he test for definiteness under 35 U.S.C. 112, second paragraph, is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.' *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)", and goes on to further explain "[i]f one skilled in the art is able to ascertain ... the meaning of the terms ...[at issue] in light of the specification, 35 U.S.C. 112, second paragraph, is satisfied." Additionally, "[s]ome latitude in the manner of expression and the aptness of terms should be permitted even though the claim

language is not as precise as the examiner might desire", and further encourages examiners "to suggest claim language to applicants to improve the clarity or precision of the language used", but explains examiners "should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement." See, MPEP section 2173.02.

In view of the foregoing, Applicants respectfully assert the term " $C_{6-10}$ aryl" satisfies the definiteness requirement of 35 U.S.C. 112 because those skilled in the art would, in view of the specification, understand the metes and bounds of the term " $C_{6-10}$ aryl" and therefore readily understand what Applicants are claiming. Accordingly, Applicants respectfully request the Office to withdraw this rejection.

With regard to " $C_{2-6}$ heteroaryl", Applicants direct the Office's attention to page 4, line 25 wherein Applicants explain as follows:

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

Applicants further direct the Office's attention to page 2, lines 9-10, which indicates, "The term " $C_{m-n}$ " or " $C_{m-n}$  group" used alone or as a prefix, refers to any group having m to n carbon atoms." In view of the foregoing, the "2-6" in the term " $C_{2-6}$ heteroaryl" indicates the number of carbons—and not atoms—present in a  $C_{2-6}$ heteroaryl. That is, a  $C_{2-6}$ heteroaryl contains from 2 to 6 carbons. The 2-6 carbon range, however, does not account for the one or more heteroatoms that may also be present. For example, the definition provided for a five-membered heteroaryl indicates that 1, 2 or 3 ring atoms may be selected from N, O, and S. If 1 ring atom is an N, O, or S, the remaining 4 ring atoms are carbon (4 carbon atoms + 1 hetero atom = 5 membered heteroaryl), i.e. thienyl. If 2 ring atoms are selected from N, O, and S, the remaining 3 ring atoms are carbon (3 carbon atoms + 2 hetero atoms = 5 membered heteroaryl), i.e. thiazolyl. If 3 ring atoms are selected from N, O, and S, the remaining 2 ring atoms are carbon (2 carbon atoms + 3 hetero atoms = 5 membered heteroaryl), i.e. triazolyl.

In view of the foregoing, Applicants respectfully request the Office to withdraw this rejection.

**Rejections under 35 U.S.C. §112, first paragraph**

Claims 1, 2, 8, 13, and 19 are rejected under 35 U.S.C., first paragraph, "because the specification, while being enabling for certain compounds corresponding to formula (I) or (III), it does not reasonably provide enablement for the long list of potential groups R<sub>1</sub>." The Office further asserts, "In particular the prophetic heterocycles of 'C<sub>2-6</sub>heteroaryl' nor the optional substituents on R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> & R<sub>5</sub>." The Office's conclusion rests on its evaluation of the factors set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants, however, respectfully assert a proper evaluation and balancing of the Wands factors does not lead to the Office's conclusion, but rather leads to a finding that the claims at issue are enabled. Applicants will address each Wands factor in the same order as the Office.

**Breadth of the claims:** The Office states, "The claims are very broad encompassing a variety of heterocycles, bearing multiple substitutions."

Applicants, however, respectfully assert when assessing the "breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims." MPEP section 2164.08. "How a teaching is set forth, by specific example or broad terminology, is not important." *Id.* Indeed, "[c]laims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious." *Id.*

Applicants assert the 3 schemes set forth at page 18, line 4 to page 20, line 2 are directed to processes for making compounds well within the level of ordinary skill in the art at the time the presently claimed invention was filed and the scope of such schemes is commensurate in scope with the breadth of the claims at issue. Applicants further demonstrated via the 9 exemplified compounds and various intermediates set forth therein that these 3 schemes can be successfully used to prepare compounds in accordance with the presently claimed invention. Applicant note, however, that examples are not needed to support every contemplated substituent group because as the Court has recognized, such a requirement "would not serve the constitutional purpose of promoting progress in the useful arts". *Id.* (citing *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976)). Applicants respectfully assert in view of the

knowledge of a person of ordinary skill in the art, the specification as filed, and the constitutional purpose of promoting progress in the useful arts, Applicants have enabled the entire scope of the claims at issue.

### **Nature of the Invention**

The Office asserts, "This is a medicinal chemistry invention requiring the synthesis of compounds and these compounds must have the utility of treating pain or as ligands at opioid receptors."

Applicants, however, respectfully assert the presently claimed invention is directed to non-peptide delta opioid receptor agonists having high (nanomolar/subnanomolar) affinity for  $\delta$  receptors and low (micromolar) affinity for both  $\mu$  and  $\kappa$  that are useful in treating at least one disease/disorder associated with the  $\delta$  receptor. Such diseases/disorders include, but are not limited to anxiety, pain, and functional gastrointestinal disorders.

### **State of the Art, Amount of direction provided by the inventor, level of predictability in the art, existence of working examples, quantity of experimentation needed to make or use the invention.**

The Office asserts, "While little information was given in the specification, the examiner would like to point the applicant's attention to the tables 1 and 2 (pg. 24), which reveal the level of activity at the  $\delta$ ,  $\kappa$  and  $\mu$  opioid receptors for only nine compounds." The Office then proceeds to enter into a very confusing discussion of what the Office has deduced "is meant by 'activity' or 'inactivity'" via a variety of references.

Applicants respectfully assert the Office's attention should be directed to Applicants' specification and not references discussing the activity of ligands that are not within the scope of the presently claimed invention and/or not directed to binding to the same receptor. To that end, Applicants direct the Office's attention to the biological assays described in the specification at page 21, line 4 to page 24, line 15 and Tables 1 and 2. Specifically, Applicants direct the Office's attention to the paragraph set forth at page 21, lines 5-15 wherein Applicants expressly state:

*The compounds of the invention are found to be active towards  $\delta$  receptors in warm-blooded animal, e.g., human. Particularly the compounds of the invention are found to be effective  $\delta$  receptor ligands. In vitro assays, infra, demonstrate these surprising activities, especially with regard to agonists potency and efficacy as demonstrated in the rat brain functional assay and/or the human  $\delta$  receptor functional assay (low). This feature may be related to in vivo activity and may not be linearly correlated with binding affinity. In these in vitro assays, a*

compound is tested for their activity toward  $\delta$  receptors and  $IC_{50}$  is obtained to determine the selective activity for a particular compound towards  $\delta$  receptors. In the current context,  $IC_{50}$  generally refers to the concentration of the compound at which 50% displacement of a standard radioactive  $\delta$  receptor ligand has been observed.

(emphasis added). Applicants further point to the data set forth in Tables 1 and 2, which demonstrate compounds encompassed by the presently claimed invention have high (nanomolar/sub-nanomolar)  $\delta$  receptor binding affinity and lower  $\mu$  and  $\kappa$  receptor binding affinity. Applicants respectfully assert the publications cited by the Office fail to provide an iota of evidence that would have led a person of ordinary skill in the art to doubt compounds encompassed by the presently claimed invention would have activity across the full scope of what is claimed.

Applicants respectfully assert that although the presently claimed invention is directed to non-peptide  $\delta$  opioid receptor agonists, the Office relies on 1) statements in Calo et al. indicating a peptide (UFP-101) that is an NOP receptor antagonist designed to antagonize NOP receptors did not bind to opioid receptors (See Calo et al., point 5 abstract and Results page 305; 2) statements in Chang et al. indicating DADLE, a peptide not expected to be active at  $\kappa$ -sites, was not active at  $\kappa$ -sites but rather was active at benzomorphan sites; 3) comments in Erchegeyi et al. directed to binding affinities of sst<sub>4</sub>-selective Somatostatin (SRIF) agonist peptides—not nonpeptidic  $\delta$  opioid receptor agonists— for five-membrane receptor sub-types (sst<sub>1</sub>, sst<sub>2</sub>, sst<sub>3</sub>, sst<sub>4</sub>, and sst<sub>5</sub>) known to modulate SRIF activity—not  $\delta$ ,  $\kappa$ , or  $\mu$  opioid receptors or affinities associated therewith; 4) comments in Kruzynski et al. directed to  $\mu$  opioid receptor—not  $\delta$  opioid receptor—affinity associated with various endomorphin-2 peptide analogues; 5) comments in Carson et al. directed to tropanylidene chemotypes falling outside the scope of the presently claimed invention that exhibit  $\mu$  opioid receptor selectivity—not  $\delta$  opioid receptor selectivity—and the SAR associated therewith having “good  $\mu$  activity” (emphasis added)—not  $\delta$  activity; 6) comments in Coats et al. directed to SAR associated with tropanylidene chemotypes falling outside the scope of the presently claimed invention having high (nanomolar/subnanomolar) affinity for both  $\mu$  and  $\delta$  receptors—not high (nanomolar/subnanomolar) affinity for  $\delta$  receptors and lower affinity for both  $\mu$  and  $\kappa$  receptors; and 7) comments in U.S. Patent publication No. 2005/009860 (hereinafter the “860 publication”) directed to heteroaryl attached to the left handed phenyl—and not the piperidine Nitrogen—of a chemotype falling outside the scope of the presently claimed invention.

The Office asserts that "[g]iven the diverse behaviour and complete lack of activity for certain groups, such prophetic recitations as those of the instant claims should be evaluated carefully." The Office further assert that "[b]ased upon the sheer unpredictability of the area of opioid receptor ligands as evidenced by the prior art, and the paucity of working examples it is readily apparent that one could not make/use this very broad invention without undue experimentation."

Applicants, however, respectfully assert that undue experimentation is not required to practice the claimed invention. Applicants further assert the references relied on by the Office fail to advance adequate reasons a person of ordinary skill in the art could not use the genus as a whole without undue experimentation.

Indeed, 1) UFP-101 of Calo et al. is not involved with the "very same receptors of the instant case" as asserted by the Office; 2) Chang et al., Erchegeyi et al. and Kruzsynski et al. are not directed to nonpeptide  $\delta$  opioid receptor agonists or modulation of activity associated therewith; 3) Carson et al. is not directed to nonpeptide  $\delta$  opioid receptor agonists but rather to how the SAR of tropanylidene  $\mu$  opioid receptor agonists affects  $\mu$ —and not  $\delta$ — "activity"; 4) Coats et al. is not directed to chemotypes within the scope of the presently claimed invention having high (nanomolar/subnanomolar) affinity for  $\delta$  receptors and lower affinity for both  $\mu$  and  $\kappa$  receptors but rather to tropanylidene derivatives having high (nanomolar/subnanomolar) affinity for both  $\delta$  and  $\mu$  receptors; and 5) the '858 publication is not directed to chemotypes within the scope of the presently claimed invention and does not indicate heteroaryls attached to piperidine nitrogen will have any effect on affinity for  $\delta$ ,  $\mu$ , and/or  $\kappa$  receptors ( $R^1$  heteroaryls of Applicants' claimed invention to which this portion of the Office's discussion is directed are attached to piperidine nitrogen—and not either phenyl). As a result, the references cited by the Office would not have led a person of ordinary skill in the art to doubt s/he could use the full scope of the claimed genus without undue experimentation.

Even if the Office had identified inoperative compounds within the scope of the presently claimed invention, Applicant respectively assert such inoperatives would not render the claimed invention unenabled. Indeed, a claim may encompass inoperative embodiments and still be enabled. See, *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984), *In re Angstadt*, 537 F.2d 498, 503-3 (CCPA 1976), and *In re Cook*, 439 F.2d 730, 732 (CCPA 1971).

Furthermore, the 35 USC 112, first paragraph prohibition against undue experimentation does not ban any and all experimentation. Indeed, even voluminous research is not undue so

long as it is of a routine nature. *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Pat. Off. Bd. App. 1986). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." MPEP section 2164.06 [citations omitted].

Applicants respectfully assert the specification at hand provides ample guidance as to the direction in which experimentation for the presently claimed compounds should proceed. (See page 18, line 4 to page 20, line 2; page 21, line 4 to page 24, line 15; Tables 1 and 2; Examples 1-9; and intermediates 1-8). Additionally, persons of ordinary skill in the art routinely test compounds for activity/receptor affinity in assays, such as, those set forth in the application at issue. As any experimentation needed under the circumstance at issue—even if a large amount of experimentation—would be routine and the specification at issue provides a reasonable amount of guidance, Applicants respectfully assert undue experimentation is not required to practice the claimed invention.

Furthermore, a lack of working examples covering the full scope of the claimed invention does not, in and of itself, render the claimed invention unenabled. See, *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) ("A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." (citations omitted)). In fact, working examples are not mandatory if none actually exists and the invention is otherwise disclosed so that one skilled in the art can practice it without undue experimentation. See, *In re Borkowski et al.*, 164 USPQ 642 (Fed. Cir. 1970); *In re Gay*, 135 U.S.P.Q. 311 (C.C.P.A. 1962); *In re Stephens*, 188 U.S.P.Q. 659 (C.C.P.A. 1976); and *Ex parte Krenzer*, 199 U.S.P.Q. 227 (Pat. Off. Bd. App. 1978). See also, *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 U.S.P.Q. 409 (Fed. Cir. 1984) (holding use of "prophetic" examples or intended examples does not automatically make a patent non-enabling merely because there can be no guarantee the examples will actually work). Moreover, Applicants "are not required to disclose every species

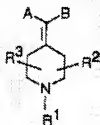
encompassed by their claims even in an unpredictable art" for a generic claim to be fully enabled. See, *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976).

As Applicants have provided 9 Examples within the scope of the claimed invention, 3 schemes commensurate in scope with the full breadth of what is being claimed, several biological assays, and the binding affinity data generated in at least one disclosed assay for a representative sampling of compounds within the scope of the presently claimed invention, Applicants respectfully assert a person of ordinary skill in the art in view of what s/he comes to the patent with will be able to make and use the full scope of the claimed invention without undue experimentation. Accordingly, Applicants respectfully assert the claims at issue are enabled and therefore respectfully request the Office to withdraw this rejection.

**Rejections Under 35 U.S.C. § 103(a)**

Claims 1-5, 8, 13, and 19-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 6,187,792 or US 6,455,545, or WO 98/28275 in view of Wei, et al. and in further view of Iddon et al. See, Non final Office Action mailed May 14, 2008 (hereinafter "Office Action") at page 3. Applicants point out that the '792 and '545 patents are U.S. counterparts of WO 98/28275. Furthermore, the '545 patent is a continuation of the '792 patent. As a result, whatever Applicant asserts with respect to the '792 patent also applies to the '545 patent and vice versa. Additionally, whatever Applicants assert as to the '792 and/or '545 patent also applies to the WO 98/28275 and vice versa.

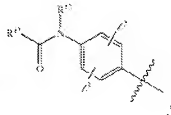
The Office asserts "the most compelling is the suggestion of the generic disclosure that reverse amides are preferred substituents as shown below (taken from pages 3-4 of WO9828275),



(I)

[wherein]

A is selected from



See, Office Action at pages 4-5.

Applicants, however, respectfully assert the Office has failed to establish a prima facie case of obviousness because an element of the claim is missing. Indeed, while WO 98/28275



defines the A and B groups disclosed therein to include a multitude of possible substituent groups, WO 98/28275 fails to define either A, or B to include a phenyl meta-substituted with a -N(R')C(=O)R" group. As is clearly evident upon viewing the claims at issue, there are two phenyl groups, one having a -C(=O)NR'R" group para-substituted thereon and another having a -N(R')C(=O)R" meta-substituted thereon. The invention disclosed in WO 98/28275, however, clearly fails to disclose a phenyl meta-substituted with a -N(R')C(=O)R" group. This deficiency is not satisfied by Wei et al.

The Office asserts Wei et al. "teaches that while the phenyl ring bearing the dialkylamide group was important for activity, other features in particular the substituents on the other phenyl ring (i.e. the methoxy group of SNC-80) were less sensitive to changes and that preparing compounds with such modifications would likely be the right place to look for more potent compounds." *Id.* at page 5. The Office then asserts the "author's own word" are as follows:

"Initial SAR studies<sup>15</sup> around SNC-80 indicated that the 4-N,N-diethylaminocarbonyl group is a key structural feature, but neither the methoxy group, the allyl group, nor the two methyl groups on the piperazine were essential for high affinity at the  $\delta$  opioid receptor that does not bear the is a site ripe for modification." (pg. 2895 column 2)

*Id.* (Applicants were unable to locate the following portion of the quoted language, "that does not bear the is a site ripe for modification...", and respectfully assert the noted language was erroneously included in the quotation.) The Office further emphasized the following sentence in another block quote of Wei et al.: "Considerable variation is possible in the nature of substitution on the phenyl ring, and this can lead to some highly potent  $\delta$  agonists." *Id.* at page 5.

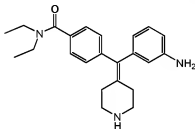
Applicants, however, respectfully assert the Wei et al. language relied on by the Office is nothing more than an invitation to go fishing. Wei et al.—like WO 98/28275—fails to identify a single compound with or without the exact core of the presently claimed invention containing a phenyl group with a para-substituted -C(=O)NR'R" group AND a meta-substituted -N(R')C(=O)R". Again, this deficiency is not satisfied by Iddon et al.

The Office asserts that "Iddon et al. teach that in the field of opioid receptor ligands the conversion of amino group to amide is a well-known and desirable modification", and directs Applicants' attention to the following passage of Iddon et al.: .

Separation of the desirable pain-killing properties of the opioid analgesics from their less desirable side-effects, such as addiction, respiratory depression, and tolerance, has become an achievable goal following recognition that some compounds can exhibit specificity for the different opioid receptors.<sup>1</sup> Reports (e.g. refs. 2 and 3) that opioid activity has been observed with some amides of diverse chemical structure prompted us to synthesize an amide derivative (1) of benzomorphan and to convert the oximes whose syntheses are described in our preceding paper<sup>4</sup> into the corresponding amides, (3), (6), and (10).

The Office is apparently

attempting to conjure up the missing meta-substituted  $-N(R')C(=O)R''$  group from compound 60 set forth Table 1 at page 3898 of Wei et al. Compound 60 has the following structure



Applicants, however, respectfully assert the chemical structures of the compounds to which the comments of Iddon et al. are directed are completely different not only from the chemical structure of the presently claimed compounds, but also from the structures of the compounds of Wei et al. Furthermore, Iddon et al. does not “teach that in the field of opioid receptor ligands the conversion of amino group to amide is a well-known and desirable modification.” Rather, Iddon et al. details the conversion of an oxime substituent group to an amide group—not the conversion of an amino to an amide. Moreover, Iddon et al. provides no data indicating such conversion met with improved opioid affinity for any receptor—let alone improved affinity for the  $\delta$  receptor and decreased affinity for the  $\mu$  and  $\kappa$  receptors. As a result, a person of ordinary skill in the art would have had no reason to believe the converted compounds of Iddon et al. had any opioid receptor affinity—let alone improved affinity for the  $\delta$  receptor and decreased affinity for the  $\mu$  and  $\kappa$  receptors. In fact, the absence of such data would likely lead a person of ordinary skill in the art to infer Iddon et al. produced compounds having decreased opioid receptor affinity than the starting compounds.

As Iddon et al. is 1) directed to compounds having a completely different chemical scaffold, 2) directed to converting an oxime—not an amino—of such very chemically different compounds to an amide, and 3) devoid of any data indicating these very chemically different converted compounds had any affinity for any opioid receptor—let alone improved affinity for the

$\delta$  receptor and decreased affinity for the  $\mu$  and  $\kappa$  receptors as a result of such conversion—a person of ordinary skill in the art would have had no reasonable expectation that combining Wei et al. and Iddon et al. in the manner suggested by the Office would produce compounds having the high affinity for the  $\delta$  receptor and low affinity for the  $\mu$  and  $\kappa$  receptors of the presently claimed compounds.

Applicants further assert the Office has failed to establish a *prima facie* case of obviousness because the Office has failed to identify why a person of skill in the art would have culled the particular substituent groups out of WO 98/28275 in the manner suggested by the Office and then further modified this pieced together genus in view of Wei et al and Iddon et al. in the manner needed to arrive at Applicants' claimed invention. Indeed, establishing a *prima facie* case of obviousness as to chemical compounds requires the Office "to identify *some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie case of obviousness of a new claimed compound.*" *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.*, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. June 8, 2007) (emphasis added). Instead, the Office appears to be using impermissible hindsight to reconstruct Applicants' claimed invention. As a result, Applicants respectfully assert the Office's *prima facie* case of obviousness further fails because the Office has failed to identify why a person of ordinary skill in the art would have pieced together Applicants' claimed invention from WO 98/28275 in view of Wei et al. and Iddon et al. in the manner suggested by the Office.

In view of the foregoing, Applicants respectfully assert the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request the Office to withdraw this rejection.

#### **Double Patenting**

Claims 1-5, 8, 13, [and] 19-23 are rejected on the ground of nonstatutory obviousness-type double patenting as "being unpatentable over claims 1-4, 6 [and] 8 of U.S. 6,187,792 in view of Wei, Z. et al. ...[and] Iddon et al. ...."

Claims 1-5, 8, 13, [and] 19-23 are rejected on the ground of nonstatutory obviousness-type double patenting as "being unpatentable over claims 1-4 [and] 6 of U.S. 6,455,545 in view of Wei, Z. et al. ...[and] Iddon et al. ...."

Claims 1-5, 8, 13, [and] 19-23 are rejected on the ground of nonstatutory obviousness-type double patenting as "being unpatentable over claims 1-4, 6, 7, 13, 19, [and] 22 of U.S. 6,693,117, in view of Wei, Z. et al. ...[and] Iddon et al. ...."

Applicants respectfully request the Office to withdraw each of the above referenced nonstatutory obviousness-type double patenting rejections for the same reasons as already articulated hereinabove as to the same references.

Claims 1-5, 8, 13, [and] 19-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as "being unpatentable over claims 1-5, 8 [and] 15-18 of copending Application No. 10/596,850, in view of U.S. 6,187,792 and Wei, Z. et al. ...." The Office asserts the "claims of the instant case differ from those of the '850 application in the identity of R1. At least where R1 is phenyl or H (Formula III) of the instant case, the alkyl, cycloalkyl, and H derivatives of the '850 application are equivalents as taught by the secondary references."

The application at hand is the earlier filed of the two pending applications at issue, and therefore Applicants respectfully request the Office to withdraw this rejection upon withdrawal of all other rejections at issue. Applicants note when "a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer." MPEP section 804 at paragraph I. B.1.

The Office requested Applicants point out co-pending diphenylmethylen-4-piperidine applications. Applicants note the following issued AZ patents directed to diphenylmethylen-4-piperidines: U.S. Patent Nos. 6,187,792; 6,455,545; 6,753,335; 6,756,387; 6,693,117; 6,838,468; 7,022,715; 7,074,808; 7,205,317; and 7,312,336. Applicants also note the following co-pending AZ patent applications directed to diphenylmethylen-4-piperidines: U.S. Patent Application Nos. 10/533,838; 10/541,656; 10/541,664; 10/550,661; 10/555,980; 10/555,981; 10/557,067; 10/557,068; 10/557,069; 10/596,853; 10/596,850; 11/575,841; 11/875,014; and 11/951,014. Applicants further note the following discontinued AZ patent applications directed to diphenylmethylen-4-piperidines: 10/477,854.

### **Conclusion**

In view of the foregoing amendments and/or remarks, Applicants respectfully assert the claims are in condition for allowance, and therefore respectfully solicit a Notice of Allowance. In order to expedite disposition of this case, the Office is invited to contact Applicants' representative at the telephone number below to resolve any remaining issues.

Although Applicants believe no fees in addition to the 1-month extension of time that accompanies this response are due, the Commissioner is hereby authorized to

charge any deficiency in the fees or credit any overpayment(s) to deposit account No. 26-0166, referencing Attorney Docket No. 100952-1P US.

Respectfully submitted,

/Jacqueline M. Cohen/

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